Docket No.: 312762002400
(PATENT)

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Dated: 8/25/03 Signature: _____ (Michael Boyd)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Norimitsu SAITO and Ming ZHAO

Application No.: 09/734,786 Group Art Unit: 1636

Filed: December 11, 2000 Examiner: D. Sullivan

For: METHODS FOR INTRODUCING GENES INTO MAMMALIAN SUBJECTS

APPELLANT'S BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This brief is in furtherance of the Notice of Appeal, filed in this case on June 25, 2003.

The fees required under § 1.17(f) and any required petition for extension of time for filing this brief and fees therefor, are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief is transmitted in triplicate.

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I. REAL PARTY IN INTEREST

Anticaner, Incorporated of 7917 Ostrow Street, San Diego, California, 92111 is the real party in interest and sole assignee of the present application by virtue of the assignment recorded at reel 012037, frame 0145.

II. RELATED APPEALS AND INTERFERENCES

There are no pending appeals or interferences known to Appellant, Appellant's undersigned attorney, or assignee that are related to or would be affected by a decision by the Board of Patent Appeals and Interferences in the presently pending appeal.

III. STATUS OF CLAIMS

Claims 1-21 were originally filed. Claims 9, 10, 12, 16, 18, 20, and 21 were cancelled and claims 11, 15, and 19 were amended in the Amendment filed January 3, 2003. Pending claims 1-8, 11, 13-15, 17 and 19 were finally rejected under 35 U.S.C. 112, first paragraph, for allegedly lacking enablement, in the Office action mailed March 25, 2003. Applicants appeal the final rejection of the pending claims.

IV. STATUS OF AMENDMENTS

Applicants filed a Response After Final Rejection and a Notice of Appeal on June 25, 2003. No claim amendments were made in the Response After Final Rejection. The Examiner responded to the Response After Final Rejection with an Advisory Action mailed July 21, 2003. In the Advisory Action, the Examiner indicated that Applicants' response would not be sufficient to place the claims in condition for allowance. No amendments were filed subsequent to the final rejection. Thus, the claims that appear in the Appendix are the claims as pending.

V. SUMMARY OF INVENTION

The invention relates to the discovery that histocultured tissue can be genetically modified *ex vivo* and transplanted into a mammalian subject (Specification, page 2, line 25 to page

3, line 15). Data presented in the specification indicate that the success of the *ex vivo* genetic modification is enhanced by treating the histocultured tissues with collagenase (Specification at page 11, line 10 to page 14, line 5). Another aspect of the invention relates to transplanting into the dermis of a subject at least one hair follicle that has been modified *ex vivo* to contain an exogenous nucleic acid molecule (Specification at page 14, line 7 to page 15, line 8).

VI. ISSUE

The sole issue on appeal is, would one of ordinary skill in the relevant art be able to practice the claimed invention without having to engage in undue experimentation.

VII. GROUPING OF CLAIMS

Applicants request that the pending claims be adjudicated in the following groups:

Group I: comprising claims 1-8, 11, 13 and 14, which recite methods of *ex vivo* tissue modification and transplanting of that modified tissue into a subject; and

Group II: comprising claims 15, 17, and 19, which recite methods of *ex vivo* tissue modification.

Rejected claims 1-8, 11, 13-15, 17 and 19 do not stand or fall together. The claims of Group I relate to *ex vivo* modification and transplantation of modified tissue. In contrast, the claims of Group II, which recite *ex vivo* methods of tissue modification, do not recite a transplantation step. Claim groups I and II should be adjudicated separately because each group of claims involves a different question of enablement.

A determination of enablement for one group of claims will not adequately evaluate whether the remaining group is fully enabled because the claim groups encompass different subject matter. For example, if a claim from Group II were evaluated and found to be fully enabled, the question of whether Applicants had enabled the claimed transplantation procedure would not be addressed. Alternatively, if a claim of Group I was found to lack enablement because methods of

tissue transplantation were not fully enabled, the enablement of the Group II claims would not have been properly reviewed because these claims do not recite transplantation.

To properly ascertain whether the pending claims are adequately supported by an enabling disclosure, it is necessary to determine separately whether the claimed methods of ex vivo modification and tissue transplantation are enabled. Because the subject matter recited in the two groups of claims differ, the claims of Groups I and II should stand or fall separately.

VIII. ARGUMENT

The present appeal addresses the single issue of whether the pending claims lack enablement under 35 U.S.C. 112, first paragraph. "To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation' ... Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *See In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Moreover, enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

In the present case, claims 1-8, 11, 13-15, 17 and 19 stand rejected for allegedly lacking enablement. In the first Office action, the Examiner interpreted the nature of the invention as being "directed to *ex vivo* gene therapy." Office action mailed October 3, 2002, page 7. The Examiner interpreted the claims to be "specifically drawn to a composition and methods for therapeutic or vaccination purposes . . . ." *Id.* The Examiner then discussed how challenging the field of gene therapy was at the time the present application was filed. The pending claims were then rejected because the alleged relevant art (gene therapy) was so unpredictable and that the specification was so devoid of guidance as to require one of ordinary skill in the art to engage in undue experimentation to practice the claimed invention. Applicants respectfully disagree.

Applicants understand that claims are to be given their broadest reasonable scope during prosecution. *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Nevertheless, the broadest reasonable scope of the claims must be consistent with the interpretation that one of ordinary skill in the art would reach. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999). Moreover, it is improper to read limitations from the written description into the claims. *Prima Tek II, L.L.C. v. Polypap, S.A.R.L.*, 318 F.3d 1143, 1148 (Fed. Cir. 2003). Nevertheless, the Examiner's interpretation of the claimed subject matter as being specifically drawn to gene therapy methods for therapeutic or vaccination purposes misinterprets the pending claims.

One of ordinary skill in the art would readily interpret the pending claims as being directed to methods of genetically modifying tissue *ex vivo* and transplantation of that modified tissue into a mammalian host. The skilled artisan would also recognize that the pending claims do not recite nor do they require that the *ex vivo* genetic modification produce a therapeutic effect in a host after transplantation. At most, all the claims require is that the genetic modifications encompassed by the claimed invention merely function as intended to achieve the goals of the claimed methods. Because the claims do not recite a therapeutic effect for the genetic modification or the transplantation, the Examiner has erred in reading such a requirement into the pending claims.

The pending claims, properly interpreted, relate to methods of genetically modifying tissue *ex vivo* and transplantation of that modified tissue into a mammalian host. Contrary to the allegations of the Examiner, one of ordinary skill in the relevant art would readily be able to practice the full scope of the claimed subject matter without undue experimentation. Guidance regarding how to practice the claimed invention is found throughout the specification as originally filed.

Prior art methods of *ex vivo* genetic tissue modification are discussed in the Background section of the specification and provide guidance to a skill artisan regarding how to practice the full scope of the claimed invention. For example, the Background section discusses experiments where an albino point mutation in the mouse tyrosinase gene was corrected *ex vivo* (Specification at page 1, lines 17-20, citing *Nature Biotechnol* (1998) 16:1343-1346). *Ex vivo* genetic modification of hair

follicles is also discussed in the Background section (Specification at page 1, lines 23-25, citing *Nature Med* (1995) 1:705-706).

Ex vivo modification and transplantation is also discussed in the Background section of the specification. For example, work with mutant skin keratinocytes from patients with lamellar ichthyosis that were successfully modified *ex vivo* and then transplanted into nude mice to obtain a normal epidermis is discussed (Specification at page 2, lines 1-5, citing *Nature Med* (1996) 2:1263-1267). The Background section of the specification also refers to work with keratinocytes that were cultured individually *in vitro*, genetically modified, and then transplanted into nude mice to obtain reformed tissue (Specification at page 2, lines 5-8, citing *Nature Biotechnol* (1997) 15:1388-1391). All of these efforts by skilled artisans indicate that methods for modifying tissue *ex vivo* to introduce exogenous nucleotide samples as well as methods of transplanting that modified tissue were well known in the art at the time the present application was filed.

Perhaps the most compelling guidance regarding how to practice the claimed invention is provided in the specification's working rather than prophetic examples. Specifically, Example 1 discloses detailed guidance regarding the acquisition and *ex vivo* genetic modification of tissue (*i.e.*, hair follicles) (Specification at page 11, line 10 to page 14, line 5). In this series of experiments, mice hair follicles were obtained, histocultured, and genetically modified *ex vivo* to express the green fluorescent protein (GFP) in culture. These experiments and the actual results obtained indicate how the methods encompassed by the pending claims provide an improved method of making *ex vivo* genetic modifications.

Example 2 provides detailed guidance regarding how one of ordinary skill in the art would take tissue genetically modified *ex vivo* and transplant that tissue into a recipient (Specification at page 14, line 7 to page 15, line 8). In this example, tissue was obtained and modified to express GFP according to the methods described in Example 1. The modified tissue was then introduced into a mammalian host. The modified and transplanted tissue was shown to contain a transferred gene that was active in the host recipient for at least 10 days after transplantation. This series of experiments provides ample guidance to one of ordinary skill in the

relevant art regarding how to genetically modify tissue *ex vivo* and to transplant that tissue without undue experimentation.

Examples 3-8 describe an alternative method to genetically modify tissue *ex vivo* (Specification at page 15, line 10 to page 20 line 18). In these examples, a retroviral vector was generated that expressed the *Streptomyces antibioticus* tyrosinase gene. The retroviral vector was transfected into a packaging cell line to produce virus particles (Examples 3 and 4). Expression of the retroviral vector's tyrosinase gene was confirmed using a variety of assay methods, which were discussed in detail (Examples 5 and 6). Tissue was obtained, cultured according to the methods of the invention, and modified *ex vivo* to express the exogenous genes present in the retroviral vector (Example 7). Expression of the exogenous genes was then confirmed (Example 8). This series of examples serves to provide the skilled artisan an alternative method with which to modify tissue *ex vivo* for transplantation.

The pending claims are fully supported by the ample amount of knowledge available in the relevant art when the present application was filed and the guidance provided in the specification. As discussed in the Background section of the specification, methods of genetic *ex vivo* tissue modification and transplantation of that tissue were well known in the art. Moreover, the specification itself provides detailed guidance, particularly in the form of working examples, regarding how to modify tissue samples *ex vivo* and how to transplant those tissue samples into a mammalian host. Applicants submit that the knowledge available in the art taken with the detailed disclosure of the specification is more than sufficient to allow one of ordinary skill in the art to practice the full scope of the claimed invention without undue experimentation. Accordingly, the pending claims are fully enabled.

IX. CLAIMS INVOLVED IN THE APPEAL

The Appendix contains a copy of the claims on appeal.

X. CONCLUSION

All of the claims pending are directed to methods of making genetic modifications to tissue *ex vivo* or modifying and then transferring the modified tissue to a mammalian host. The Examiner has not accurately interpreted the pending claims nor has any substantive basis for rejecting the pending claims for lack of enablement been advanced by the Examiner. Claims 1-8, 11, 13-15, 17 and 19 are in condition for allowance and passage of these claims to issuance is respectfully requested.

Dated: August 25, 2003

Respectfully submitted,

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APPENDIX

Claims Involved in the Appeal of Application Serial No. 09/734,786

1. A method to introduce a nucleic acid molecule into a mammalian subject which method comprises

transplanting into the dermis of said subject at least one hair follicle that has been modified *ex vivo* to contain said nucleic acid molecule.

2. The method of claim 1 wherein said hair follicle has been modified *ex vivo* in a histoculture.

3. The method of claim 2 wherein said histoculture has been treated with collagenase prior to modifying said hair follicle.

4. The method of claim 1 wherein said hair follicle is in anagen.

5. The method of claim 1 wherein said follicle has been modified to contain said nucleic acid molecule by transducing with said nucleic acid or by lipofection.

6. The method of claim 1 wherein said follicle has been modified to contain said nucleic acid molecule by treating with a viral vector.

7. The method of claim 6 wherein said viral vector comprises the supernatant of a viral packaging cell, and/or wherein said viral vector comprises a retroviral vector, and/or wherein said viral vector comprises an adenoviral vector.

8. The method of claim 1 wherein said mammal is a mouse or a human.

11. (Amended 1/3/03) A method to introduce a nucleic acid molecule into a mammalian subject which method comprises transplanting into the corresponding tissue of said mammal a histocultured intact tissue that has been modified *ex vivo* to contain said nucleic acid molecule;

wherein said histoculture has been treated with collagenase prior to modifying said tissue with the nucleic acid.

13. The method of claim 11 wherein said modifying with nucleic acid comprises treating said tissue with a liposomal composition, or wherein said modifying comprises transducing the cells of said tissue with said nucleic acid, or wherein said modifying comprises treating said tissue with a viral vector.

14. The method of claim 11 wherein said intact tissue is dermis, or wherein said tissue is lymph tissue.

15. (Amended 1/3/03) A method of delivering a nucleic acid to a hair follicle which method comprises maintaining said hair follicle in histoculture and treating said histoculture with a nucleic acid;

wherein said treating with a nucleic acid is preceded by the step of treating said histoculture with collagenase.

17. (Amended 1/3/03) A method of delivering a nucleic acid to an intact tissue which method comprises treating a histoculture of said intact tissue with said nucleic acid;

wherein said treating with a nucleic acid is preceded by the step of treating said histoculture with collagenase.

19. (Amended 1/3/03) The method of claim 17 wherein said tissue is skin or lymphoid.